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ORIGINAL ARTICLE

Association between obesity after liver transplantation and steatosis, inflammation, and fibrosis of the graft

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Abstract

Background: Nonalcoholic steatohepatitis has become one of the leading causes of liver transplantation. The development of steatosis, as well as the link to inflammation and fibrosis, after transplantation remain poorly understood. The aim of this analysis was to evaluate the influence of obesity on histopathological changes of the graft during long-term follow-up.

Methods: A total of 1494 longitudinal liver biopsies of 271 recipients were evaluated during a follow-up period of 5 to 10 years. Clinical and laboratory parameters as well as histopathological categories of steatosis, inflammation, and fibrosis were explored by routine protocol biopsies.

Results: The BMI and prevalence of diabetes mellitus significantly increased after transplantation ($P < .01$). Diabetes and de novo obesity were significantly associated with the degree of graft steatosis. There was no correlation between former steatosis and inflammation or fibrosis. Inflammation was a precursor of fibrosis, and fibrosis increased over the first 3 years ($P < .01$). No severe graft dysfunction was observed.

Conclusion: Obesity and diabetes mellitus correlated with higher grades of steatosis and de novo steatosis after transplantation. Metabolic syndrome must be considered as a serious post-transplant complication that can cause histopathological alteration. However, the progress from steatosis to steatohepatitis is not as common as expected.

KEYWORDS
diabetes, fibrosis, metabolic complications, metabolic syndrome, obesity

1 | INTRODUCTION

During the last decades, advanced surgical techniques and immunosuppressive therapy have led to excellent survival after liver transplantation. The survival rates reach up to 83% after 1 year, 61% after 10 years, and 41% after 20 years.[1] However, there is an increase in medical complications unrelated to the graft, such as de novo malignancies, recurrence of the underlying disease, metabolic complications, and cardiovascular diseases.[2-7] Cardiovascular factors cause 19%-42% of all deaths after liver transplantation. The individual cardiovascular risk profile is thought to be affected by metabolic syndrome, which is at least partially associated with immunosuppressive therapy.[2,4,7,8] Metabolic syndrome is defined by obesity, dyslipidemia, arterial hypertension, and hyperglycemia, and

is one of the most frequent post-transplant complications. Its prevalence after transplantation ranges from 44% to 58% according to different studies.[4,8-12] The hepatic manifestations are nonalcoholic fatty liver disease (NAFLD) ranging from asymptomatic steatosis to nonalcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC). NASH is gaining more and more importance as the reason for end-stage liver disease in the future and will concern most of those patients with severe liver disease until 2030. Twenty percent of all patients with NASH have been reported to develop cirrhosis and require liver transplantation.[13-17] After transplantation, NAFLD has up to 60% risk of recurrence or appears as a de novo development as a part of the metabolic syndrome.[15,18] Recurrence of or de novo NAFLD in transplant recipients may have an impact on transplant outcomes. However, little is known about the progress of steatosis toward inflammation and fibrosis of the graft. Therefore, we performed an analysis of sequential histological parameters such as steatosis, inflammation, and fibrosis in a transplant population in order to deliver more information and determine the relevance based on protocol biopsies in a high-volume transplant center.

2 | PATIENTS AND METHODS

Between January 1, 2005, and June 30, 2011, 816 liver transplantations were performed in 705 patients at our clinic. All patients were followed up according to the routine program at our outpatient department. We included adult patients with a minimum follow-up of 5 years after transplantation to guarantee at least two liver biopsies during the follow-up period. Twenty-one patients (3.0%) were excluded because of incomplete histological sequence including less than two protocol biopsies or due to lost follow-up. A total of 239 patients (33.9%) had died before the time of analysis and were, therefore, excluded. Thirty-one patients (4.4%) were further excluded as they were under 18 years of age. As retransplantation was mainly performed due to initial non-function, the last liver transplantation was considered eligible if the criterion for the histological follow-up was fulfilled. The overall retransplantation rate was 13.6% and affected 111 patients at least once, of which 66 patients died. Thus, a cohort of 414 patients was identified to be suitable for the histological analysis, including 369 (89.1%) patients with first transplant, 43 patients (10.4%) with second transplant, and 2 (0.5%) patients with a third liver transplant.

Routine examinations were performed at 1, 3, 5, 7, and 10 years after transplantation, including blood tests, radiography, sonography examinations, and a percutaneous biopsy. Patients on anticoagulation (n = 143) were excluded from the analysis because their histological follow-up was considered incomplete due to bleeding risk, leaving a cohort of 271 patients for further histological analysis. Routine biopsies were performed percutaneously on the right lobe. Data were extracted from a prospectively organized database and a digital patient's documentation system. Clinical data included age, sex, median follow-up time, underlying disease, retransplantation, MELD-score (Model End-Stage Liver Disease), BMI (body-mass-index = weight[kg]/height[m^2]), prevalence of diabetes mellitus, donor's age, donor's sex, donor's BMI, ischemic time, viral reinfection (given only for patients with viral hepatitis), and recurrence of alcohol abuse (given only for patients with alcohol-induced liver disease). Obesity was defined as a BMI ≥ 30 kg/m^2. De novo diabetes mellitus was defined as the development of diabetes during the first 5 years after transplantation. De novo obesity was defined as weight gain corresponding to a BMI > 30 kg/m^2 during the first 5 years.

A total of 1494 biopsies (at least 2 per patient) were evaluated by experienced pathologists. The following standardized information was extracted from the written report. Presence of steatosis was classified as no steatosis (grade 0), mild (5%-10%, grade 1), moderate (11%-25%, grade 2), high (26%-50%, grade 3), and severe (>50%, grade 4) based on the pathological classification.[19] The grading of steatosis was adapted according to the given percentage and, therefore, was similar over the years from 2005 to 2011. Inflammation was graded according to the scoring system of Desmet and Scheuer (none: 0; minimal: 1; mild: 2; moderate: 3; and severe: 4). Fibrosis was staged from 0 to 4 (0: absent; 1: mild without septa; 2: moderate with few septa; 3: numerous septa without cirrhosis; and 4: cirrhosis).[20,21] De novo steatosis was defined as the development of grade 2-4 steatosis during the first 5 years after transplantation. De novo steatohepatitis was defined as the development of steatosis grade 2-4 in combination with higher grades of inflammation (2-4) and ballooning of hepatocytes during the first 5 years. Noninvasive techniques, such as transient elastography, were not routinely performed.

Patients were grouped according to the underlying disease: alcoholic steatohepatitis and NASH to steatohepatitis; HBV- and HCV-associated cirrhosis to viral cirrhosis; primary biliary cirrhosis and primary sclerosing cholangitis to cholestatic disorders; Wilson's disease, oxalosis, amyloidosis, and alpha-1-antitrypsin-deficiency to genetic and enzymatic disorders; and all other remaining patients to other rare indications group (including autoimmune hepatitis, tumors, polycystic disease, Budd-Chiari-syndrome, Osler's disease, acute liver failure, and unknown cirrhosis). As there were only three patients with a pre-transplant diagnosis of NASH, making a statistical analysis was not feasible; therefore, we grouped these three patients with the steatohepatitis group due to similar histopathological pathogenesis.

The primary end point was the influence of BMI on the histopathological changes of the graft in terms of steatosis, fibrosis, and inflammation during long-term follow-up. Secondary end points were the correlation between clinical and demographic parameters and the development of steatosis, fibrosis, or inflammation of the graft.

Statistical analysis was performed using SPSS (IBM Statistics version 25.0). Nominal data were assessed using cross-tables (Fisher's exact test). Non-normally distributed data were tested using the Mann–Whitney U test and Kruskal–Wallis test. Subgroup analysis was performed according to the groups of underlying diseases: steatohepatitis, viral hepatitis, and cholestatic disorders. The groups of metabolic disorders and others were not analyzed due to

heterogeneity and small patient numbers. The level of significance was set at 0.05.

The study was conducted according to the principles of good scientific practice and the Declaration of Helsinki. As patients' data were directly anonymized and retrospectively evaluated, the study was exempted from institutional review board approval.

3 | RESULTS

Demography: A total of 414 patients were eligible for analysis. Demographic data of patients included in the study are provided in Tables 1 and 2. There were 250 (60.4%) men and 164 (39.6%) women with a median age of 54 years (20-74 years) at the time of transplantation. The median follow-up period was 9 years (6-12 years). A total of 104 (25.1%) patients had diabetes mellitus at transplantation. The median BMI at transplantation was 26 kg/m^2 (16-43 kg/m^2), and the median MELD-score was 16 (range, 6-40). The majority of patients (92.3%) obtained calcineurin inhibitor-based immunosuppression. Twelve (2.9%) patients were weaned from immunosuppressive therapy during follow-up. Twenty (4.8%) patients received monotherapy with mycophenolate mofetil. Steroids were administered for the first 56 days after transplantation and then withdrawn. None of the patients received long-term glucocorticoids. Alcohol relapse was documented in 34 (20.4%) patients, ranging from sporadic alcohol intake to heavy drinking. Thirty-eight (74.5%) patients developed recurrent viral hepatitis.

Most of the patients had steatohepatitis (41.1%) as the underlying disease, followed by viral cirrhosis (24.4%), cholestatic disorders (12.1%), genetic and enzymatic defects (4.8%), and other rare diseases (17.6%). There were 3 patients (0.7%) who had nonalcoholic steatohepatitis and 167 (40.3%) had alcoholic steatohepatitis. HCC was detected in 107 (25.8%) patients.

Forty-five (10.9%) patients underwent retransplantation due to initial non-function, severe dysfunction frequently due to hepatic

TABLE 1 Demographic data of the cohort

	N = 414
Gender (male/female)	250 (60.4%)/164 (39.6%)
Age at LT [years]	54 (20-74)
Median follow-up [years]	9 (6-12)
Retransplantation	45 (10.9%)
Split organ transplantation	20 (4.8%)
Diabetes mellitus at LT	104 (25.1%)
BMI at LT [kg/m^2]	26 (16-43)
MELD-score at LT	16 (6-40)
Immunosuppression	
Immunosuppression free	12 (7.7%)
Tacrolimus	340 (82.1%)
Tacrolimus + MMF	38 (9.2%)
Cyclosporin A + MMF	4 (1.0%)
MMF	20 (4.8%)
Relapse of alcohol abuse	34 (20.4%)
Viral recurrence	38 (74.5%)
Donor's characteristics	
Donor's age [years]	52 (8-90)
Donor's gender (male/female)	210 (50.7%)/201 (48.6%)
Donor's BMI [kg/m^2]	25 (15-46)
Cold ischemic time [min]	556 (18-1499)
Total ischemic time [min]	608 (36-1633)
De novo obesity after 5 y	128 (30.9%)
De novo diabetes mellitus after 5 y	101 (24.4%)
De novo steatosis after 5 y	81 (29.9%)
De novo steatohepatitis after 5 y	21 (8.0%)

Note: Frequencies are given in absolute numbers and percentage. Parametric data are given as median and minimum-maximum.
Abbreviation: LT: liver transplantation; MMF: mycophenolate mofetil. N = 414.

TABLE 2 Overview of underlying disease

		N = 414
Steatohepatitis N = 170	Nonalcoholic steatohepatitis	3 (0.7%)
	Alcoholic steatohepatitis	167 (40.3%)
Viral Hepatitis N = 101	Hepatitis B	27 (6.6%)
	Hepatitis C	74 (17.8%)
Cholestatic disorders N = 50	Primary or secondary biliary disease	25 (6.0%)
	Primary or secondary sclerosing cholangitis	20 (4.8%)
	Benign recurrent cholestatic disease	5 (1.2%)
Genetic and enzymatic defects N = 20	Wilson's disease	1 (0.2%)
	Oxalosis	7 (1.7%)
	Amyloidosis	4 (1.0%)
	Alpha-1-antitrypsin-deficiency	5 (1.2%)
Others N = 73	Autoimmune hepatitis	9 (2.2%)
	Tumor	8 (1.9%)
	Polycystic disease and Caroli syndrome	31 (7.5%)
	Budd-Chiari syndrome	4 (1.0%)
	Osler's disease	1 (0.2%)
	Acute liver failure	2 (0.4%)
	Unknown Cirrhosis	18 (4.3%)
Hepatocellular Carcinoma at time of LT		107 (25.8%)

Note: Frequencies are given in absolute numbers and percentage. Parametric data are given as median and minimum-maximum.
Abbreviation: LT, liver transplantation. N = 414.

artery thrombosis, or ischemic type biliary disease; however, no retransplantations were due to graft failure due to steatohepatitis or recurrent NASH. Fifteen (33.3%) patients with a retransplant had alcohol-induced steatohepatitis as the underlying disease for the first transplant, but none were diagnosed with NASH. Twenty (4.8%) patients received a split organ transplantation. A total of 210 (50.7%) male and 201 (48.6%) female grafts were transplanted, with a median donor age of 52 years (8-90 years) and a donor BMI of 26 kg/m^2 (16-43 kg/m^2). The information on donor's sex was missing in 3 cases. The median cold ischemic time was 556 min (18-1499 min), and the median total ischemic time was 608 min (36-1633 min).

The BMI significantly as well as the prevalence of diabetes mellitus increased until the fifth year after transplantation (Figure 1). De novo obesity had a prevalence of 30.9% (n = 128) and de novo diabetes mellitus of 24.4% (n = 101). Routine biopsies were evaluated for 271 patients. We found de novo steatosis in 81 (29.9%) patients and de novo steatohepatitis in 21 (8.0%) patients.

Histology: The number of patients presenting higher grades (2-4) of steatosis increased over time but not significantly (Figure 2). There was a significant increase in fibrosis (stage 2-4) and inflammation (grade 2-4) until the third year (Figure 2). Excluding patients with viral recurrence, patients with higher grades of steatosis during the first year after transplantation were not at a significantly higher risk of developing higher grades of inflammation or stages of fibrosis until the tenth year (Figure 3).

Obesity did not significantly correlate with the development of post-transplant steatosis, inflammation, or fibrosis until the fifth year (Figure 4). Patients with higher grades of steatosis 5 years after transplantation showed a significantly higher prevalence of diabetes mellitus, whereas there was no significant correlation between diabetes prevalence and the development of inflammation or fibrosis (Figure 4). To evaluate the risk of de novo obesity, we grouped patients into those with overweight at transplantation (obesity), normal weight (no obesity), and de novo obesity. Patients with de novo obesity were at a significantly higher risk of developing higher grades of steatosis, inflammation, and stages of fibrosis until the 10th year after transplantation (Figure 5).

To clarify the dynamics of histopathological changes, we differentiated between de novo steatosis and patients with a stable grade of steatosis. The demographic data for de novo steatosis are given in Table 3. Prevalence *of* de novo diabetes mellitus was significantly higher in the group with a stable grade of steatosis (P = .02). We found a significant correlation between steatohepatitis (39.7% vs. 50.0%, P = .02), a higher BMI (25 (16-37) kg/m^2 vs. 26 (18-40) kg/m^2, P = .02), and a higher prevalence of pre-transplant diabetes mellitus (18.5% vs. 31.3%, P = .03), and the development of de novo steatosis 5 years after transplantation.

A demographic subgroup analysis was performed for 21 patients with de novo steatohepatitis. Five (23.8%) patients were females, and 16 (76.2%) were males. Seven (33.3%) patients suffered from alcoholic steatohepatitis, 6 (28.6%) patients from viral hepatitis, 5 (4.8%) patients with cholestatic disorders, and one patient had a Budd-Chiari-syndrome, one an unknown cirrhosis, and one a polycystic disease. Six (28.6%) patients had developed HCC at the time of transplant, and 4 (19.0%) patients underwent retransplantation. The median age of patients with de novo steatohepatitis was 49 years (28-66 years) and the median BMI of 26 (20-34); 4 (19.0%) patients presented with diabetes at the time of transplant. There were no alcoholic relapses and only one recurrent viral infection within the de novo steatohepatitis group. Four (19.0%) patients with de novo steatohepatitis showed de novo obesity, and 4 (19.0%) developed de novo diabetes mellitus 5 years after transplantation.

4 | DISCUSSION

This analysis evaluated the influence of BMI on the liver graft in terms of steatosis, fibrosis, and inflammation during long-term follow-up. BMI and prevalence of diabetes mellitus significantly increased after transplantation (Figure 1). The rate of de novo obesity was 30.9%. Previous reports confirmed that over 15% of patients with normal weight become obese during the first year and over 25% within 3 years.[4] Immunosuppression, obesity in recipients and donors before transplant, marital status, and correction

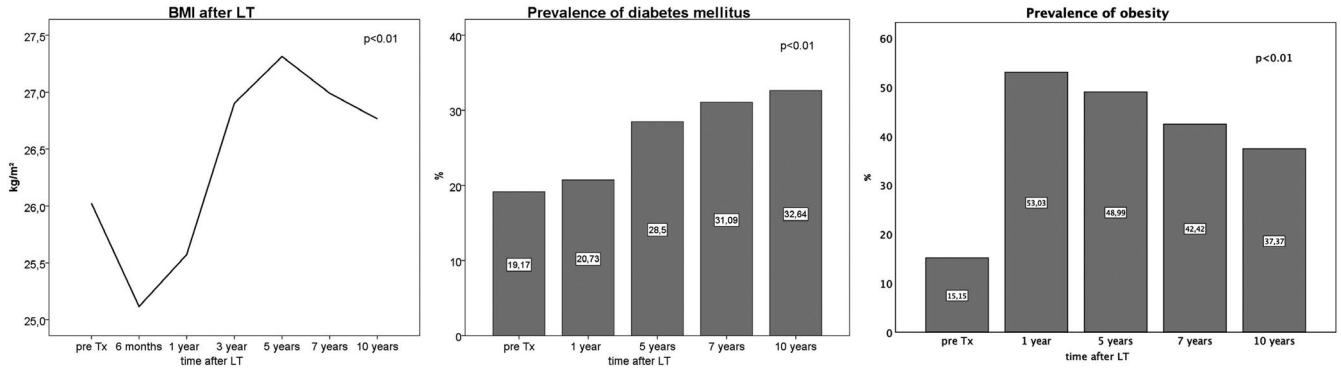

FIGURE 1 Development of BMI, diabetes and obesity after transplantation. Display shows development of BMI value (kg/m^2) and the prevalence of post-transplant diabetes (%) and obesity (%). Prevalence is given as percentage according to the y-graph and absolute numbers within the bars. Obesity is defined as BMI ≥ 30 kg/m^2. "pre Tx" defined as directly before liver transplantation. Abbreviatios: BMI: body-mass-index, LT: liver transplantation. N = 271

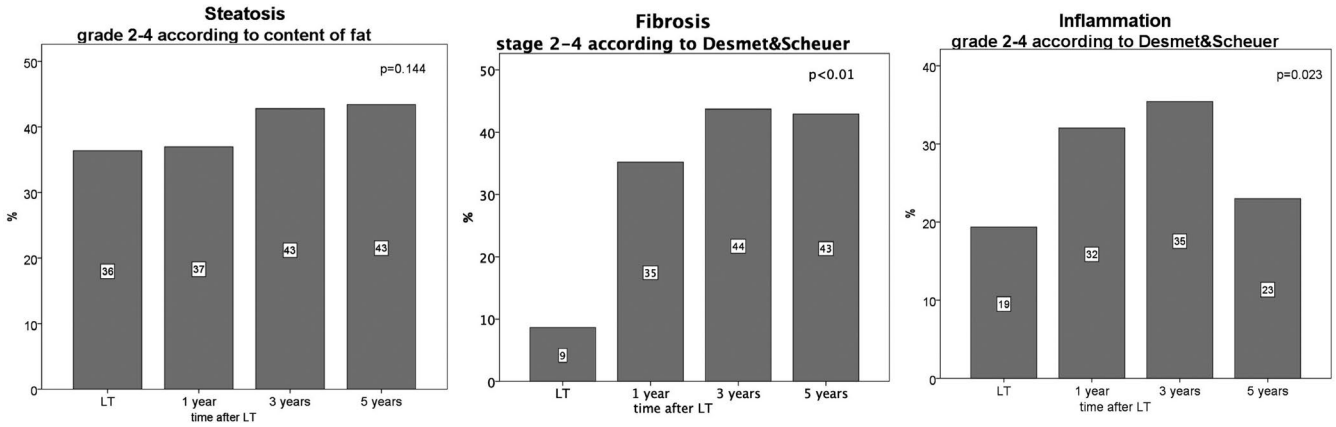

FIGURE 2 Development of the prevalence of steatosis, fibrosis and inflammation after transplantation. Prevalence is given as percentage according to the y-axis and absolute numbers within the bars. Abbreviations: LT: liver transplantation. N = 271

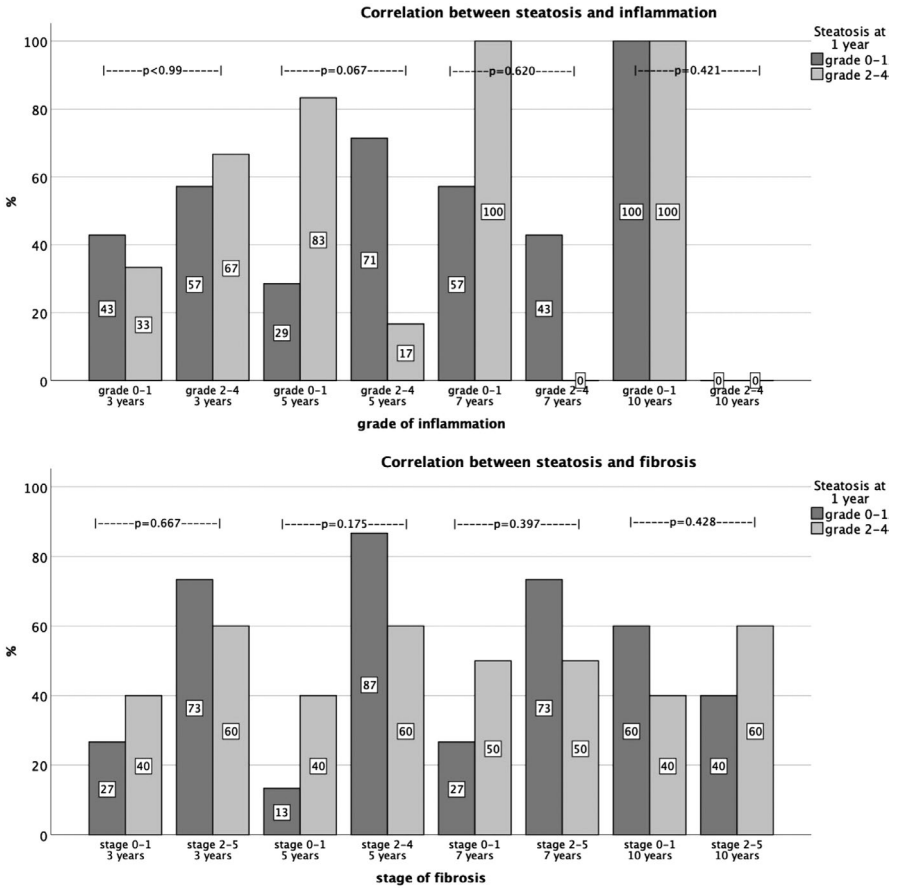

FIGURE 3 Correlation between histopathological differentiations. There is no correlation between the higher grades of steatosis within the first year after transplantation and the development of inflammation (first line) or fibrosis (second line) until the 10th year after. Prevalence is given as percentage according to the y-axis and absolute numbers within the bars. Patients with viral recurrence were excluded (n = 36). N = 235

of catabolic status have been previously described as specific risk factors.[4,12,18,22,23]

Glucocorticoids are associated with weight gain, but the influence of calcineurin inhibitors is still under discussion. Both reduce beta-cell secretion, whereas steroids additionally increase insulin resistance.[17,24] New-onset diabetes after transplantation has an incidence ranging from 14% to 44%.[4,25-28] We identified a significantly increasing prevalence of diabetes mellitus and a rate of 24.4% for new-onset diabetes (Figure 1). However, as the majority of our patients received tacrolimus, we were not able to

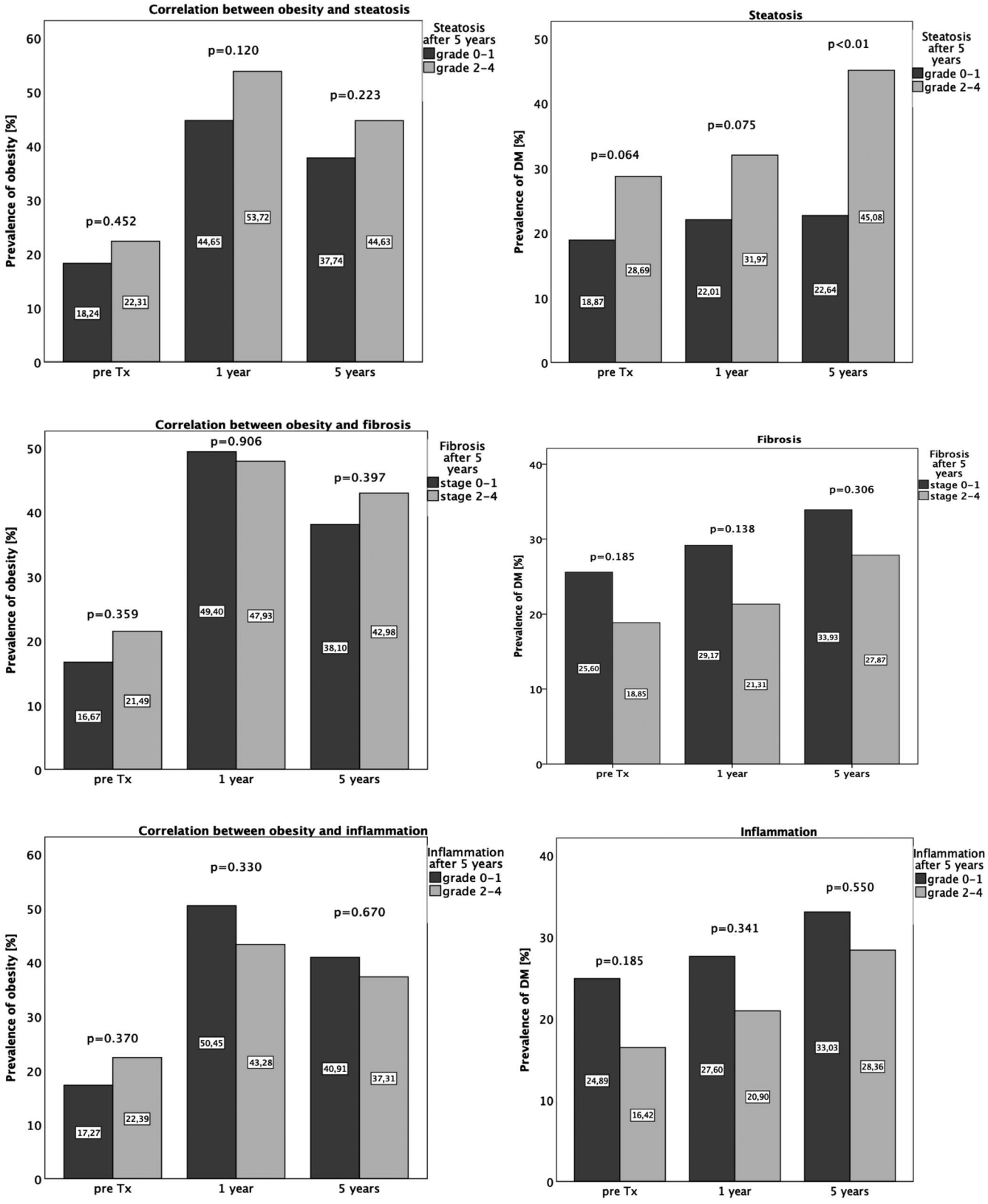

FIGURE 4 Relation between obesity, diabetes and histopathological differentiation. Obesity and DM are given "pre Tx" defined as directly before liver transplantation and at the date of biopsy 1 year and 5 years after liver transplantation. Prevalence is given as percentage according to the y-axis and absolute numbers within the bars. Obesity is defined as BMI ≥ 30 kg/m^2. Abbreviations: BMI: body-mass-index; DM: diabetes mellitus, LT: liver transplantation. N = 271

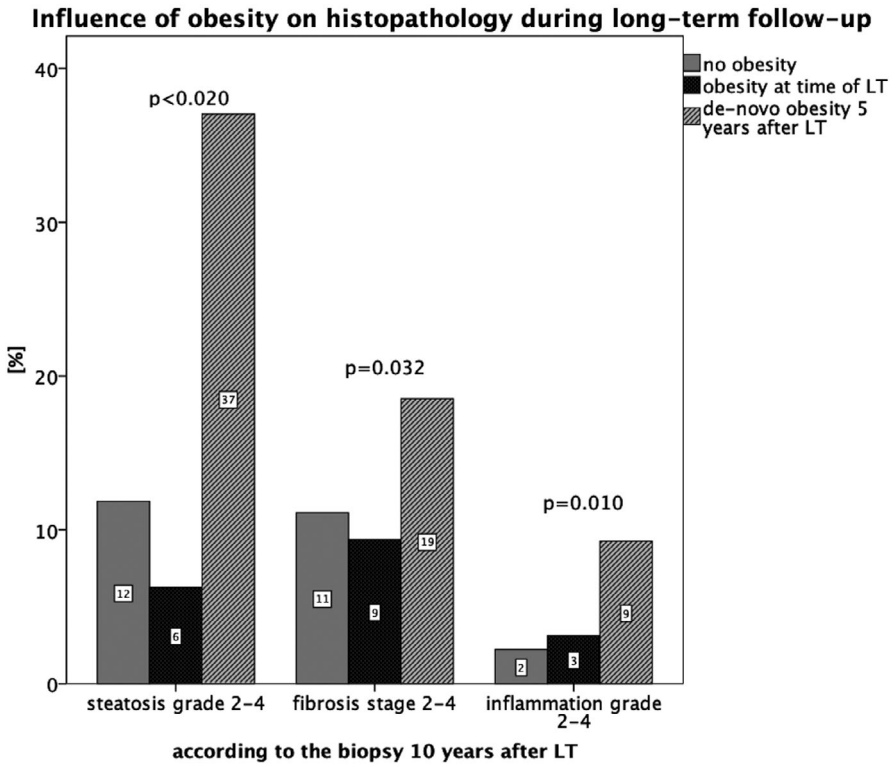

FIGURE 5 Influence of de novo obesity on histopathology. There was a significant correlation between de novo obesity after transplantation and the development of higher grades of steatosis, inflammation and stages of fibrosis 10 years after transplantation. Prevalence is given as percentage according to the y-axis and absolute numbers within the bars. Abbreviaton: LT: liver transplantation. N = 271

answer the question of immunosuppressive influence on obesity and diabetes.

Previous histopathological studies have demonstrated that steatosis, steatohepatitis, and advanced fibrosis are associated with alcohol relapse, as the graft is more prone to alcohol-mediated damage.[29-34] The percentage of alcohol relapse in the group of de novo steatosis compared to the control group was not significantly different and corresponded to the findings of other authors that nearly a fifth of patients will relapse after transplant.[29-34] There might be a negative effect, but the number of 7 patients (17.5%) with de novo steatosis compared to 17 (22.6%) patients in the control group might be too small for a relevant statistical statement and the confirmation of former data.

NAFLD and NASH can be considered hepatic manifestations of metabolic syndrome.[4,12,18] There is a risk of 20%-40% for de novo NAFLD and 10% for de novo NASH in liver recipients.[18,35] In comparison, we found steatosis in 43.4% patients, de novo steatosis in 30.3% patients, and de novo steatohepatitis in 8.0% patients of our cohort at 5 years of follow-up. Reasons for de novo NAFLD or NASH are metabolic syndrome, significant post-transplant weight gain, high BMI before transplantation, and vascular comorbidity.[36-38] A higher BMI and diabetes at transplant, steatohepatitis as underlying disease, and new-onset diabetes were significantly associated with de novo steatosis in our patients after 5 years (Table 3). Various studies have identified an increased BMI as the main risk factor for steatosis of the graft.[39-42] The group of patients with de novo steatosis also included 15 patients with primary viral hepatitis, which might influence histopathological findings. However, there was no significant demographic difference between the groups, whereas we did not correct this issue during analysis. Furthermore, we did not prove the progression from steatosis to fibrosis or inflammation during our observation period (Figure 3). The limitation of this study was probably the interval of 10 years to be able to demonstrate this fact. A longer time period would be necessary to answer this correlation. However, patients with post-transplant de novo obesity were at a higher risk for steatosis, fibrosis, and inflammation until the 10th year after transplant (Figure 5). Furthermore, 239 deceased patients were excluded from analysis with 40.6% of steatohepatitis as the underlying disease. This percentage is comparable to the percentage of steatohepatitis within the analyzed group. However, due to a median survival of 4.49 (0.5-13.5) years, a histopathological comparison of patients deceased and alive would be only reasonable for a short follow-up directly after transplant and not for the long-term follow-up as intended in this analysis.

BMI, diabetes, and steatosis are raising issues after liver transplantation. We found a positive association between diabetes and de novo obesity and between higher grades of steatosis and de novo steatosis. However, we could not show that steatosis led to the inflammation or fibrosis, but we conclude, that de novo obesity

TABLE 3 Demographic of subgroup analysis

	Total cohort N = 190	De novo steatosis N = 81	*P*-value
Gender (male/female)	115/75 (60.5%/39.5%)	52/29 (64.2%/35.8%)	.59
Age at LT [years]	53 (21-74)	54 (28-68)	.55
Median follow-up [years]	9 (6-12)	10 (6-12)	.75
Underlying disease			**.02**
Steatohepatitis (n = 117)	76 (40.0%	41 (50.6%)	
Viral hepatitis (n = 69)	54 (28.4%)	15 (18.5%)	
Cholestatic disorders (n = 32)	24 (12.6%)	8 (9.9%)	
Metabolic defects (n = 12)	12 (6.3%)	–	
Others (n = 43)	24 (12.6%)	17 (21.0%)	
Hepatocellular Carcinoma at LT	53 (27.9%)	16 (19.8%)	0.17
Retransplantation	19 (10.3%)	9 (11.3%)	0.83
Split organ transplantation	7 (3.7%)	4 (4.9%)	0.74
Diabetes mellitus at LT	34 (17.9%)	26 (32.1%)	**0.02**
BMI at LT [kg/m^2]	25 (16-37)	26 (18-40)	**0.03**
MELD-score at LT	16 (6-40)	16 (6-40)	0.69
Immunosuppression			0.61
Immunosuppression free	5 (2.6%)	3 (3.7%)	
Tacrolimus	153 (80.5%)	68 (84.0%)	
Tacrolimus + MMF	23 (12.1%)	5 (6.2%)	
Cyclosporin A + MMF	1 (0.5%)	1 (1.2%)	
MMF	8 (4.2%)	4 (4.9%)	
Relapse of alcohol abuse	17 (22.6%)	7 (17.5%)	.28
Viral recurrence	19 (35.2%)	8 (53.3%)	.42
Donor's characteristics			
Donor's age [years]	52 (12-90)	48 (17-82)	.23
Donor's gender (male/female)	93/97 (48.9%/51.1%)	44/36 (54.3%/44.4%)	.20
Donor's BMI [kg/m^2]	25 (15-46)	25 (18-35)	.80
Cold ischemic time [min]	552 (55-1140)	524 (18-1499)	.17
Total ischemic time [min]	595 (84-1185)	573 (36-1633)	.41
De novo obesity after 5 y	52 (27.4%)	18 (22.2%)	.45
De novo diabetes mellitus after 5 y	33 (17.4%)	25 (9.2%)	**.02**

Note: Subgroup analysis was conducted for all patients with routine biopsies grouped to those with de novo steatosis 5 y after liver transplantation (n = 81) compared to all other patients with routine biopsies (n = 190). Frequencies are given in absolute numbers and percentage. Parametric data are given as median and minimum-maximum.

Abbreviation: LT, liver transplantation; MMF, mycophenolate mofetil. N = 271.

may lead to higher grades of steatosis and inflammation and stages of fibrosis. Therefore, further studies are necessary to prevent post-transplant obesity and diabetes thereby, avoiding severe complications.

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AUTHOR CONTRIBUTION

Eva M Dobrindt contributed to data interpretation and drafting the article. Allex Laura contributed to data collection for statistical analysis. Akylbek Saipbaev contributed to data collection. Robert Öllinger and Wenzel Schöning contributed to critical revision of the manuscript. Johann Pratschke contributed to approval of the article. Dennis Eurich contributed to concept/design.

DATA AVAILABILITY STATEMENT

Demographic data are given in this manuscript. Detailed data can be accessed on request.

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